(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 057 829 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
06.12.2000 Bulletin 2000/49

(21) Application number: **99850097.9**

(22) Date of filing: **04.06.1999**

(51) Int Cl.[7]: **C07D 487/04**, A61K 31/519, C07D 498/04
// (C07D487/04, 239:00, 231:00)

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

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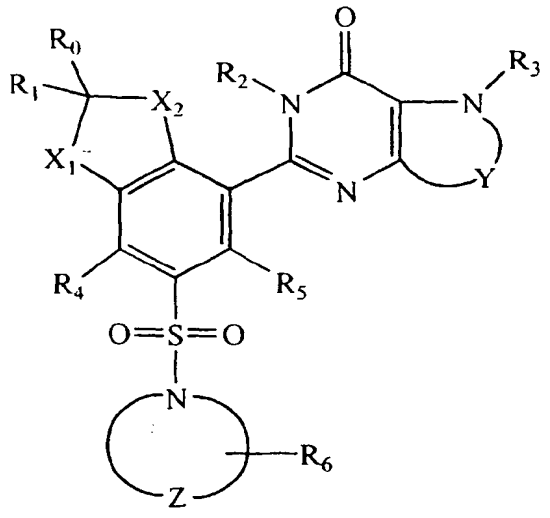
(54) Novel compounds and pharmaceutical compositions containing the same

(57) The present invention relates to novel compounds and pharmaceutical compositions containing the same. The disclosed compounds are useful for treatment of *inter alia* erectile dysfunction. They are comprised by the general formula (I) :



(I)

EP 1 057 829 A1

Description

Field of the Invention

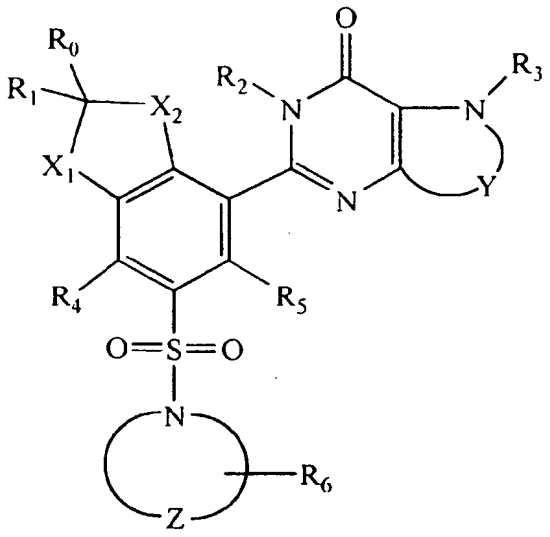
[0001] The present invention relates to novel compounds, pharmaceutical compositions containing the same as well as use of said compounds in the manufacture of a medicament for treatment of erectile dysfunction.

Background of the Invention

[0002] Erectile dysfunction is a disorder which is very common throughout the world. The recent introduction of sildenafil (the active ingredient in Viagra®) has improved the possibilities of treating this disorder significantly. Sildenafil and compounds closely related thereto are disclosed in EP 463 756, EP 702 555 and WO 98/49166 (all to Pfizer Ltd.).
[0003] However, despite the useful therapeutic properties of sildenafil, not all patients are successfully treated with this agent. Thus, there is still a great need in the art for compounds having improved therapeutic properties compared to sildenafil.

Disclosure of the Invention

[0004] There are now provided novel compounds with surprisingly improved therapeutic efficiency in comparison with the prior art cited above. In summary, the present invention relates to a compound having the general formula (I):



(I)

wherein R_0-R_6 are independently selected from at least one of a group of substituents (a)-(g) consisting of:

(a) H;
(b) straight chain, branched or cyclic saturated or unsaturated alkyl or hydroxyalkyl having 1-6 carbon atoms;
(c) O-alkyl, S-alkyl or N-$(alkyl)_n$, where alkyl is as defined in (b) and n is 1 or 2;
(d) C(O)-alkyl, O-C(O)-alkyl, S-C(O)-alkyl or NH-C(O)-alkyl, where alkyl is as defined in (b);
(e) F, Cl or Br;
(f) O-aryl;
(g) NR_8R_9, wherein R_8 and R_9 independently is H or straight chain, branched or cyclic saturated or unsaturated alkyl, C(O)-alkyl, hydroxyalkyl or O-alkyl having 1-6 carbons atoms; wherein NR_8R_9 optionally may form a five- or six-membered saturated or unsaturated ring;

wherein X_1 and X_2 are independently selected from a group of radicals consisting of:

$-C_m-$ independently substituted with the substituents (a)-(g), where m is an integer from 1 to 3 and the radical $-C_m-$ optionally may contain a double bond, ketone or thioketone functionality;

-O-;
-S-; and
-NR_{10}-, where R_{10} is H or straight chain, branched or cyclic saturated or unsaturated alkyl, C(O)-alkyl, hydroxyalkyl or O-alkyl having 1-6 carbons atoms;

wherein Y is selected from a group of radicals consisting of:
-CR_{11}=N-; -N=CR_{12}-; -N=N-; -CR_{13}=CR_{14}-; -$CR_{15}R_{16}CR_{17}R_{18}$-;
-$CR_{19}R_{20}O$-; -$OCR_{21}R_{22}$-; -$CR_{22}R_{23}NR_{24}$-;-$NR_{25}CR_{26}R_{27}$- and
-$NR_{28}NR_{29}$-, where R_{11}-R_{29} are independently selected from the substituents (a) - (g) ; wherein Z taken together with the nitrogen atom to which it is attached forms a group selected from pyrrolidinyl, piperidinyl, morpholinyl, imidazolyl, pyridinyl, pyrrolyl and 4-*N*-(R_{30})-piperazinyl, whereby R_{30} is selected from the substituents (a) - (g) ; tautomers, solvates and radiolabelled derivatives thereof; and pharmaceutically acceptable salts thereof.

[0005] As examples of pharmaceutically acceptable salts mention can be made of acid addition salts, *e.g.* a salt formed by reaction with hydrohalogen acids, such as hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic sulphonic or carboxylic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, *p*-hydroxybenzoic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, halogenbensensulphonic acid, toluenesulphonic acid and naphtalenesulphonic acid.

[0006] In a preferred embodiment of the present invention, Y is -CR_{11}=N-. R_{11} is preferably an n-propyl group.

[0007] Furthermore, it is preferred that Z taken together with the nitrogen atom to which it is attached forms a 4-*N*-(R_{30})-piperazinyl group. Preferably, R_{30} is a methyl group.

[0008] Moreover, it is preferred that X_1 is -C_m-. Preferably, m is 1. Most preferably, X_1 is -CH_2-.

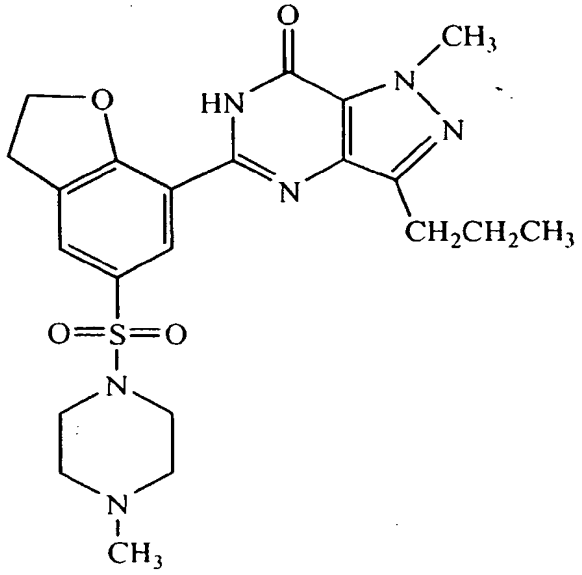
[0009] It is preferred that X_2 is -O-.

[0010] In a more preferred embodiment of the present invention, R_2 is H.

[0011] In an even more preferred embodiment, R_3 is a methyl group.

[0012] In a still even more preferred embodiment, R_4, R_5 and R_6 are all H.

[0013] In the most preferred embodiment of the present invention, said compound is 5-[2,3-dihydro-5-(4-methylpiperazin-1-ylsulfonyl)-7-benzofuryl]-1-methyl-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-d]pyrimidin-7-one, the structure of which is depicted hereinbelow. This compound is hereinafter denoted **7a.**



[0014] Furthermore, the present invention relates to a compound as set forth above for use as a pharmaceutical.

[0015] Accordingly, the present invention also relates to a pharmaceutical composition comprising a compound as set forth above as active ingredient in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

[0016] The pharmaceutical composition may be adapted for oral, intravenous, topical, intraperitoneal, nasal, buccal, sublingual or subcutaneous administration or for administration via the respiratory tract in the form of *e.g.* an aerosol

or an air-suspended fine powder. Thus, the composition may be in the form of *e.g.* tablets, capsules, powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories.

[0017] It should be noted that the composition according to the present invention may optionally include two or more of the above outlined compounds.

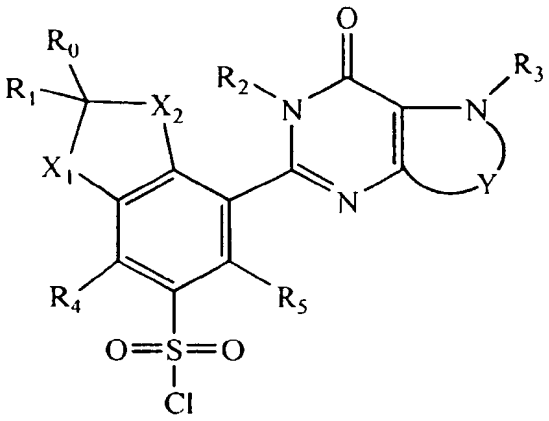
[0018] In addition, the present invention relates to the use of a compound as outlined above for the manufacture of a medicament for treatment of erectile dysfunction.

[0019] Furthermore, it is also anticipated that the compounds according to the present invention have beneficial platelet anti-aggregatory, anti-vasospastic and vasodilatory activity. Thus, they should be useful in the treatment of a number of disorders, such as angina, hypertension, congestive heart failure, peripheral vascular disease, atherosclerosis, stroke, bronchitis, asthma, allergic rhinitis and glaucoma.

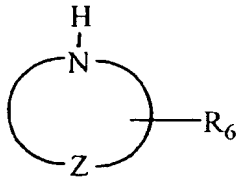
[0020] The typical dosage of the compounds according to the present invention varies within a wide range and will depend on various factors such as the individual requirement of each patient and the route of administration. The dosage is generally within the range of 0.01-100 mg/kg body weight.

[0021] The general synthetic pathway to formula (I) may be summarized as shown below (Δ=heat) :

[0022] Thus, the present invention also relates to a process for the preparation of a compound as set forth above, wherein a compound having the general formula (II) is reacted with a compound having the general formula (III), optionally in the presence of a solvent, wherein R_0-R_6 and X-Z are as defined above.

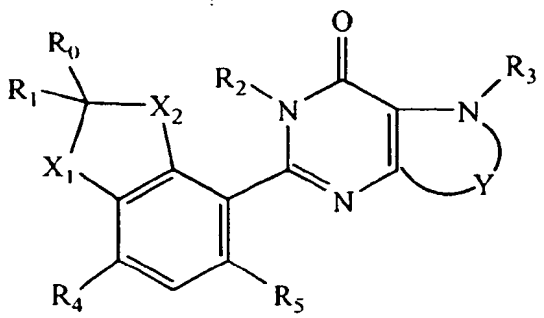


(II)



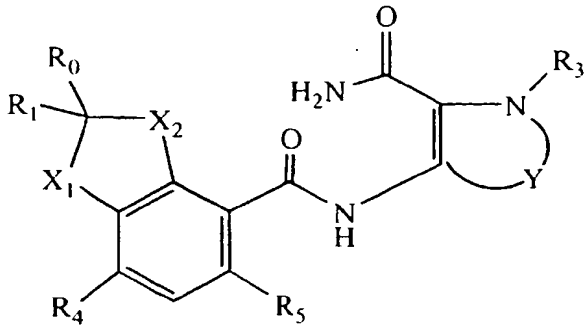
(III)

[0023] The compound (II) is prepared by reacting a compound having the general formula (IV) with $ClSO_3H$, optionally in the presence of a solvent.



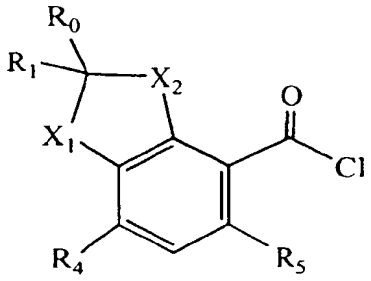
(IV)

[0024] The compound (IV) is prepared by heating a compound having the general formula (V) under basic conditions, optionally in the presence of a solvent.

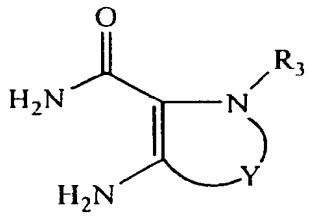


(V)

[0025] The compound (V) is prepared by reacting a compound having the general formula (VI) with a compound having the general formula (VII), optionally in the presence of a solvent and a base.



(VI)



(VII)

[0026] As for the selection of *e.g.* suitable reaction and purification conditions, useful guidance is also provided by the following publications, which are incorporated herein by reference:

[0027] DeWald, H.A., Nordin, I.C., L'Italien, Y.J., Parcell, R.F., *J. Med. Chem.*, **16**, 1346-1354 (1973);

[0028] Meyers, A.I., Reuman, M., Gabel., R.A., *J. Org. Chem.*, **46**, 783-788 (1981);

[0029] Högberg, T., de Paulis, T., Johansson, L., Kumar, Y., Hall, H., Ögren, S.O., *J. Med. Chem.*, **33**, 2305-2309 (1990).

[0030] By guidance of known reference literature, the synthesis of the starting substances (VI) and (VII) is readily accomplished by a person skilled in the art.

[0031] The present invention is further illustrated by the following non-limiting experimental part.

Brief Description of the Drawings

[0032] Fig. 1 shows a comparative study of total erection episodes as a function of dose for rats treated with **7a** and sildenafil, respectively.

[0033] Fig. 2 shows a comparative study of penile erection index as a function of dose for rats treated with **7a** and sildenafil, respectively.

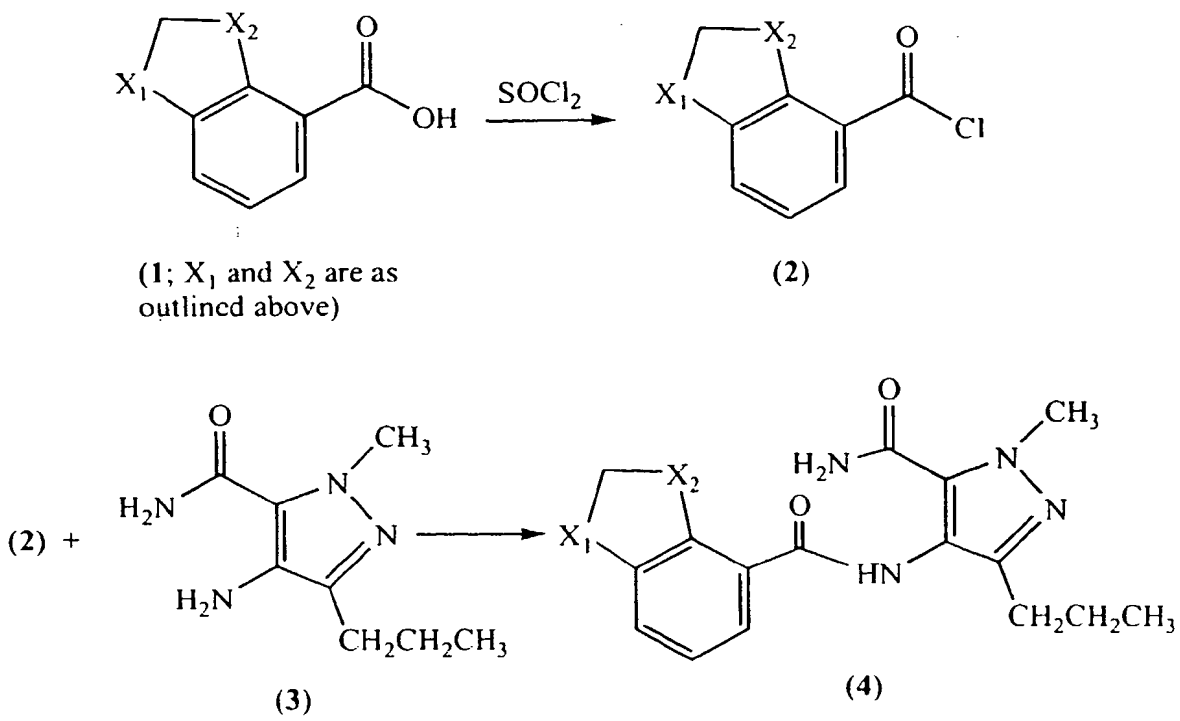
Preparation of the compounds of the present invention

[0034] Instruments used for analysis:

[0035] The melting points (m.p.) were determined on an electrothermal Mel-Temp. apparatus. They are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-WM 400 or -DPX 300 MHz spectrometer, with tetramethylsilane (TMS) as internal reference. Electron impact (EI) mass spectra were obtained using a Finnigan 731 spectrometer at 70 eV. Elemental analyses were performed at the Microanalytical Laboratory of the Chemistry Department, Al-Najah National University, West Bank.

Example 1: Preparation of compound **4**.

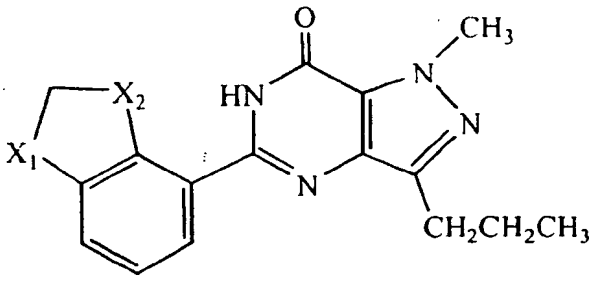
[0036]



[0037] Compound **4** was prepared by treating **1** (0.1 mole) with $SOCl_2$ in a conventional manner yielding **2**, which was then refluxed with **3** in benzene (100 ml) and NEt_3 (30 ml) for 2-3 h. The benzene was distilled off, and the solid product **4** was collected, washed with H_2O, dried and recrystallized from a suitable solvent. Yield: 82-93%.

Example 2: Preparation of compound **5**.

[0038]

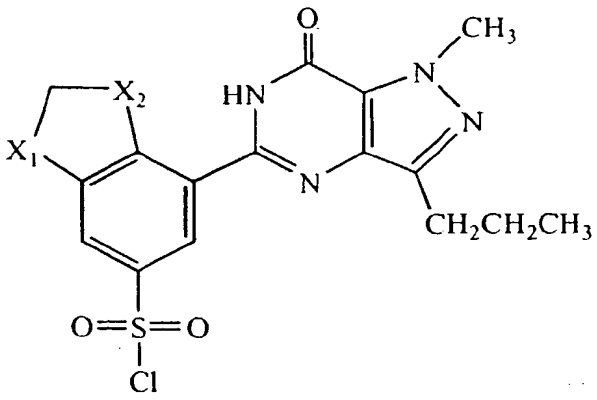


(5)

[0039] Potassium t-butoxide (0.01 mole) was added to a stirred suspension of **4** (0.01 mole) in t-BuOH (60 ml), and the resulting mixture was refluxed for 8 h. Water (40 ml) was then added, after which the solution was neutralized with diluted HCl (aq; 4%) to pH 7 and cooled. The solid product **5** was collected, washed with cold H_2O and recrystallized from a suitable solvent. The yield was 86-95%.

Example 3: Preparation of compound **6**.

[0040]

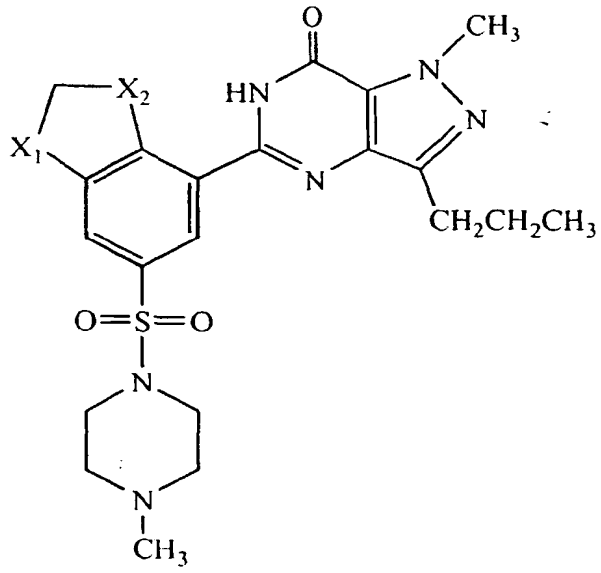


(6)

[0041] Compound **5** (0.006 mole) was added in portions to chlorosulfonic acid (4 ml) cooled to 0°C under stirring. The temperature of the reaction mixture was then allowed to rise to 25°C, followed by heating to 65-70°C for 1 h. The reaction mixture was subsequently poured onto crushed ice (50 g), after which the precipitated solid product **6** was collected and used directly in the next reaction step. Yield: 82-91%.

Example 4: Preparation of compound **7**.

[0042]



(7)

[0043] Compound **6** (0.005 mole) dissolved in THF (20 ml) was added to a solution of 1-methylpiperazine (2 ml) in THF (20 ml). The resulting mixture was stirred for 1 h at 20-25°C. The THF was distilled off, and the residue was treated with cold H_2O. The resulting white solid product **7** was collected, washed with H_2O, drained and recrystallized from a suitable solvent. Yield: 80-88%.

[0044] By following the reaction protocol above, the compounds **7a-71** listed in Table 1 below were prepared.

Table 1:

Compounds prepared, where X_1 is as specified and X_2 is -O- for all the compounds.	
Compound	X_1
7a	CH_2
7b	O
7c	S
7d	NCH_3
7e	NC_2H_5
7f	$NCH(CH_3)_2$
7g	$NC(O)CH_3$
7h	NC(O)NHPh
7i	NC(S)NHPh
7j[i)]	C=O
7k[i)]	C=S
7l[ii)]	NH

i) The compounds **7j** and **7k** were obtained after protection/deprotection of a 3-keto/thioketo group in the corresponding compounds **2j** and **2k**.

ii) Compound **7l** was obtained from **7g** by selective hydrolysis in 15% HCl for 20 min with heating.

Example 5: Detailed preparation and physical properties of **7a** and its precursors.

Preparation of 4-(2,3-dihydro-7-benzofurylamino)-1-methyl-3-propyl-5-pyrazole-carboxamide (**4a**, *i.e.* **4** wherein X_1=CH_2 and X_2=O) :

[0045] A mixture of 2,3-dihydrobenzofuran-7-carboxylic acid (1.5 g, 0.0091 mole) and $SOCl_2$ (8 ml) was refluxed (oil bath) for 3 h. Excess of $SOCl_2$ was removed *in vacuo*, and the residual acid chloride was treated with a solution of compound **1** (1.4 g, 0.0077 mole) in anhydrous benzene (25 ml), followed by addition of NEt_3 (3 ml). The solid residue was soaked in cold water (40 ml), and the remaining solid product was collected by suction filtration, drained, washed with water (2 x 20 ml) and diethyl ether (2 x 10 ml) and dried, thereby yielding **4a**. Product yield = 2.3 g (91%);
M.p. = 173-174°C;
Elemental analysis = Calculated for $C_{17}H_{20}N_4O_3$ (MW=328.37) C 62.18, H 6.14, N 17.06%. Found C 61.95, H 6.07, N 17.11%.
^{1}H NMR ($CDCl_3$) : δ 0.86 (t, J=7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.56 (m, 2H, $CH_2CH_2CH_3$), 2.46 (t, J=7.6 Hz, 2H, $CH_2CH_2CH_3$), 3.27 (t, J=8.5 Hz, 2H, C3'-H), 3.97 (s, 3H, N-CH_3), 4.73 (t, J=8.5 Hz, 2H, C2'-H), 6.94 (t, J=7.6 Hz, 1H, C5'-H), 7.34 (d, J=7.2 Hz, 1H, C4'-H), 6.26, 7.72 (2 br s, 1H each of $CONH_2$), 7.86 (d, J=8.1 Hz, 1H, C6'-H), 8.88 (br s, 1H, NHCO).
^{13}C NMR ($CDCl_3$) δ 13.7 ($CH_2CH_2CH_3$), 22.2 ($CH_2CH_2CH_3$), 27.5 ($CH_2CH_2CH_3$), 28.9 (C-3'), 39.1 (N-CH_3), 72.8 (C-2'), 114.5 (C-3), 115.6 (C-7'), 121.4 (C-5'), 128.0 (C-3'a), 129.35, 129.34 (C-4' and C-6'), 132.1 (C-4), 147.0 (C-5), 157.9 (C-7'a), 161.7 (NHCO), 165.8 ($CONH_2$).

Preparation of 5-(2,3-dihydro-7-benzofuryl)-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidine-7-one **(5a)**:

[0046] Potassium t-butoxide (0.5 g, 0.0045 mole) was added to a stirred suspension of compound **4a** (1.1 g, 0.0034 mole) in t-butanol (20 ml), and the resulting mixture was heated under reflux (oil bath) for 8 h and then allowed to cool to room temperature. Water (14 ml) was added, after which the solution was neutralized with HCl (aq; 4%; 13 ml) to pH 7, cooled to about 5-10°C, collected by suction filtration, washed with cold water (2 x 10 ml), crystallized from ethanol and dried, thereby yielding **5a.** Product yield = 1.0 g (96%);
M.p. =176-178°C (decomposition);
Elemental analysis = Calculated for $C_{17}H_{18}N_4O_2$ (MW=310.36) C 65.79, H 5.85, N 18.05%. Found C 65.72, H 5.91, N 17.93%.
^{1}H NMR ($CDCl_3$) : δ 0.99 (t, J=7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.82 (m, 2H, $CH_2CH_2CH_3$), 2.86 (t, J=7.6 Hz, 2H,

$C\underline{H}_2CH_2CH_3$), 3.22 (t, J=8.1 Hz, 2H, C3'-H), 4.19 (s, 3H, N-C$\underline{H}_3$), 4.73 (t, J=8.1 Hz, 2H, C2'-H), 6.94 (t, J=7.6 Hz, 1H, C5'-H), 7.22 (d, J=7.2 Hz, 1H, C4'-H), 8.16 (d, J=8.1 Hz, 1H, C6'-H), 10.69 (br s, 1H, N6-H).
^{13}C NMR ($CDCl_3$) : δ 14.0 ($CH_2CH_2\underline{C}H_3$), 22.2 ($CH_2\underline{C}H_2CH_3$), 27.7 ($\underline{C}H_2CH_2CH_3$), 28.9 (C-3'), 38.1 (N-$\underline{C}H_3$) , 72.6 (C-2'), 114.5 (C-3), 121.6 (C-5'), 124.4 (C-7'), 127.3, 127.5 (C-4' and C-6'), 128.1 (C-3'a), 138.5 (C-3a), 146.4 (C-5), 146.7 (C-7a), 154.0 (C-7), 156.8 (C-7'a).

Preparation of 5-(2,3-dihydro-5-chlorosulfonyl-7benzofuryl)-1-methyl-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-d] pyrimidin-7-one **(6a)** :

[0047] Compound **5a** (0.95 g, 0.003 mole) was added in portions to chlorosulfonic acid (2 ml) cooled to 0°C (ice-bath) under stirring. The resulting yellow solution was then allowed to attain room temperature and was subsequently slowly heated to 65-70°C (oil bath) for 1 h. The reaction mixture was then slowly poured onto crushed ice (25 g), whereby a white solid precipitated immediately. The white solid was filtered, dried and recrystallized from THF/petroleum ether (b.p. 40-60°C), thereby yielding **6a**.
Product yield = 1.04 g (84%);
M.p. = 221-222°C.
No elemental analysis was performed on **6a** ($C_{17}H_{17}ClN_4O_4S$; MW=408.86).
$[M]^+$=408/410 (3:1 ratio; Cl isotopic peaks);
The crude product **6a** (92% yield; m.p. 216-218°C) can be used directly in the next reaction step.

Preparation of 5-[2,3-dihydro-5-(4-methylpiperazin-1-ylsulfonyl)-7-benzofuryl]-1-methyl-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-d]pyrimidin-7-one **(7a)**:

[0048] Compound **6a** (1.25 g, 0.003 mole) was dissolved in THF (10 ml) and added to a solution of 1-methylpiperazine (1 ml) in THF (10 ml). The resulting mixture was stirred at room temperature for 1 h. The THF was then removed *in vacuo*, and the residue was treated with cold water (50 ml). The resulting white precipitate was filtered under suction, washed with water (2 x 10 ml), drained and recrystallized from 90% ethanol, thereby yielding **7a**. Product yield = 1.2 g (83%);
M.p. = 194-195°C;
Elemental analysis = Calculated for $C_{22}H_{28}N_6O_4S$ (MW=472.57) C 55.92, H 5.97, N 17.78, S 6.79%. Found C 56.00, H 6.09, N 17.51, S 6.73%.
^{1}H NMR ($CDCl_3$) : δ 0.96 (t, J=7.2 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.79 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.20 (s, 3H, N4"-C$\underline{H}_3$), 2.43 (br s, 4H, C3"-H/C5"-H), 2.85 (t, J=7.2 Hz, 2H, $C\underline{H}_2CH_2CH_3$), 3.01 (br s, 4H, C2"-H/C6"-H), 3.32 (t, J=8.5 Hz, 2H, C3'-H), 4.17 (s, 3H, N1-C$\underline{H}_3$), 4.89 (t, J=8.5 Hz, 2H, C2'-H), 7.56 (s, 1H, C4'-H), 8.54 (s, 1H, C6'-H), 10.49 (br s, 1H, N6-H). ^{13}C NMR ($CDCl_3$) δ 13.9 ($CH_2CH_2C\underline{H}_3$), 22.1 ($CH_2\underline{C}H_2CH_3$), 27.5 ($\underline{C}H_2CH_2CH_3$), 28.4 (C-3'), 38.1 (N-$\underline{C}H_3$), 45.6 (N4"-$\underline{C}H_3$), 45.9 (C-3"/C-5"), 53.9 (C-2"/C-6"), 74.0 (C-2'), 114.5 (C-3), 124.4 (C-7'), 126.2 (C-4'), 128.5 (C-6'), 129.1 (C-5'), 130.2 (C-3'a), 138.1 (C-3a), 145.2 (C-5), 146.7 (C-7a), 153.6 (C-7), 159.9 (C-7'a).

Animal experiments involving compound **7a**

[0049] The purpose of this study was to compare the biological activity of compound **7a** with that of sildenafil. In particular, the respective ED_{50}-value (ED=effective dose), erection episodes and penile erection indices of said compounds in the treatment of male rats were determined. The penile erection index is an established means of determining the erection promoting properties of a substance (see *e.g.* Ang, H.H., Sim, M.K., *Pharm. Sci.*, **3**, 117-119 (1997) and references cited therein).

[0050] In these experiments, the compounds **7a** and sildenafil were administered to male rats orally. The doses used for both drugs were 0.0781, 0.1562, 0.3125 and 0.625 mg/kg body weight. Sildenafil was dissolved in distilled water, whereas **7a** was dissolved in 1% HCl solution (aq). Control animals were administered with the vehicles only, *i.e.* distilled water or the 1% HCl solution. During the experiments, the rats were placed in glass cages for observation and had access to food and water. During 2 h after administration of the investigated compounds, the penile erection of the rats was monitored. It is worth mentioning that no copulation mounting behaviour was observed in these experiments.

[0051] The number of rats responding to this experiment protocol was recorded, and the ED_{50} results are shown in Table 2.

Table 2: Study of number (#) and percentage response as a function of dose for rats subjected to **7a** and sildenafil, respectively.

Dose[i] (mg/kg)	# Rats tested	**7a**; responding rats[ii]		Sildenafil; responding rats[iii]	
		#	%	#	%
0.0781	10	3	30	3	30
0.1562	10	4	40	3	30
0.3125	10	4	40	5	50
0.6250	10	8	80	7	70

i) No rats responded when distilled water or 1% HCl was administered.

ii) Calculated ED_{50}=0.2473 mg/kg body weight;

iii) Calculated ED_{50}=0.2843 mg/kg body weight; where the ED_{50} values are significantly different with a 95% confidence interval.

[0052] As is clear from Table 2, the ED_{50} value of **7a** is lower than that of sildenafil. Thus, a lower dose of **7a** as compared to sildenafil is required in order to elicit an erectile response.

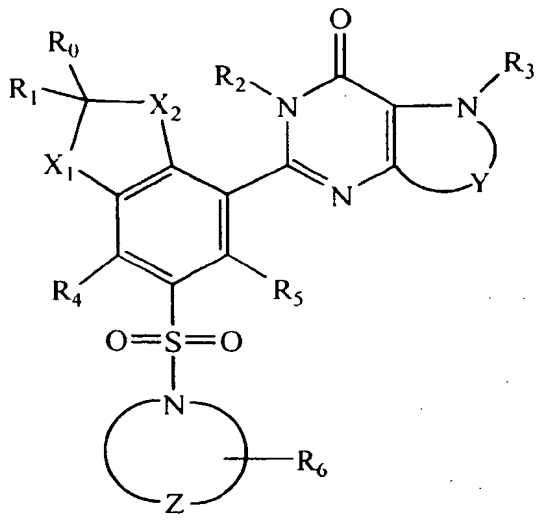
[0053] Furthermore, as for the intensity of the erectile response *per se,* the observed number of erection episodes and calculated penile erection indices substantiate that the compound **7a** is superior to sildenafil, specially at higher doses. The total number of observed erection episodes and the calculated penile erection indices are depicted in Figs 1 and 2, respectively.

[0054] Moreover, according to preliminary toxicity studies in rats, the compound **7a** is tolerated up to a dose of about 35 mg/100 kg body weight without any detrimental effects. The compound **7a** appears to be completely nontoxic and free from undesirable side-effects. Thus, high doses of **7a** provide a particularly efficient means for treatment of erectile dysfunction.

[0055] In summary, it should be clear from the present disclosure that the compounds according to the present invention are versatile new pharmaceutically active agents for the treatment of erectile dysfunction.

Claims

1. A compound having the general formula (I):



(I)

wherein R_0-R_6 are independently selected from at least one of a group of substituents (a)-(g) consisting of:

(a) H;
(b) straight chain, branched or cyclic saturated or unsaturated alkyl or hydroxyalkyl having 1-6 carbon atoms;
(c) O-alkyl, S-alkyl or N-(alkyl)$_n$, where alkyl is as defined in (b) and n is 1 or 2;
(d) C(O)-alkyl, O-C(O)-alkyl, S-C(O)-alkyl or NH-C(O)-alkyl, where alkyl is as defined in (b);
(e) F, Cl or Br;
(f) O-aryl;
(g) NR_8R_9, wherein R_8 and R_9 independently is H or straight chain, branched or cyclic saturated or unsaturated alkyl, C(O)-alkyl, hydroxyalkyl or O-alkyl having 1-6 carbons atoms;
wherein NR_8R_9 optionally may form a five- or six-membered saturated or unsaturated ring;

wherein X_1 and X_2 are independently selected from a group of radicals consisting of:

-C_m- independently substituted with the substituents (a)-(g), where m is an integer from 1 to 3 and the radical -C_m- optionally may contain a double bond, ketone or thioketone functionality;
-O-;
-S-; and
-NR_{10}-, where R_{10} is H or straight chain, branched or cyclic saturated or unsaturated alkyl, C(O)-alkyl, hydroxyalkyl or O-alkyl having 1-6 carbons atoms;

wherein Y is selected from a group of radicals consisting of:
-CR_{11}=N-; -N=CR_{12}-; -N=N-; -CR_{13}=CR_{14}-; -$CR_{15}R_{16}CR_{17}R_{18}$-;
-$CR_{19}R_{20}$O-; -O$CR_{21}R_{22}$-; -$CR_{22}R_{23}NR_{24}$-; -$NR_{25}CR_{26}R_{27}$- and
-$NR_{28}NR_{29}$-, where R_{11}-R_{29} are independently selected from the substituents (a) - (g) ;

wherein Z taken together with the nitrogen atom to which it is attached forms a group selected from pyrrolidinyl, piperidinyl, morpholinyl, imidazolyl, pyridinyl, pyrrolyl and 4-*N*-(R_{30})-Piperazinyl, whereby R_{30} is selected from the substituents (a) - (g) ;
tautomers, solvates and radiolabelled derivatives thereof; and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein Y is -CR_{11}=N-.

3. A compound according to claim 2, wherein R_{11} is an n-propyl group.

4. A compound according to any one of claims 1-3, wherein Z taken together with the nitrogen atom to which it is attached forms a 4-*N*-(R_{30})-piperazinyl group.

5. A compound according to claim 4, wherein R_{30} is a methyl group.

6. A compound according to any one of claims 1-5, wherein X_1 is -C_m-.

7. A compound according to claim 6, wherein m is 1.

8. A compound according to claim 7, wherein X_1 is -CH_2-.

9. A compound according to any one of claims 1-8, wherein X_2 is -O-.

10. A compound according to any one of claims 1-9, wherein R_2 is H.

11. A compound according to claim 10, wherein R_3 is a methyl group.

12. A compound according to claim 11, wherein R_4, R_5 and R_6 are H.

13. A compound according to claim 12, wherein said compound is 5-[2,3-dihydro-5-(4-methylpiperazin-1-ylsulfonyl)-7-benzofuryl]-1-methyl-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-d]pyrimidin-7-one.

14. A compound according to any one of claims 1-13 for use as a pharmaceutical.

15. A pharmaceutical composition comprising a compound according to any one of claims 1-13 as active ingredient in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

16. Use of a compound according to any one of claims 1-13 for the manufacture of a medicament for treatment of erectile dysfunction.

17. A process for the preparation of a compound having the general formula I as defined in any one of claims 1-13, whereby a compound having the general formula (II) is reacted with a compound having the general formula (III), optionally in the presence of a solvent,

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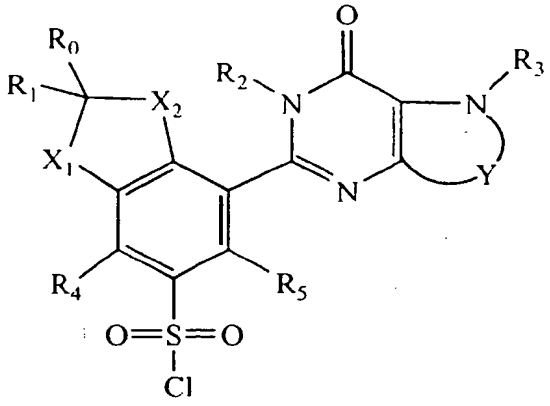
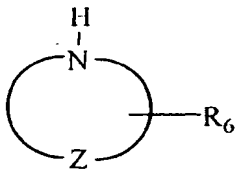


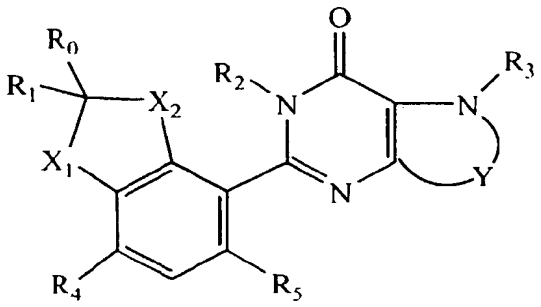
(II)



(III)

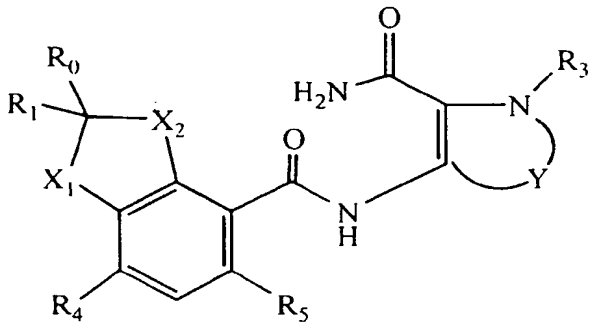
wherein R_0-R_6 and X-Z are as defined in any one of claims 1-13.

18. A process according to claim 17, whereby the compound (II) is prepared by reacting a compound having the general formula (IV) with $ClSO_3H$, optionally in the presence of a solvent.



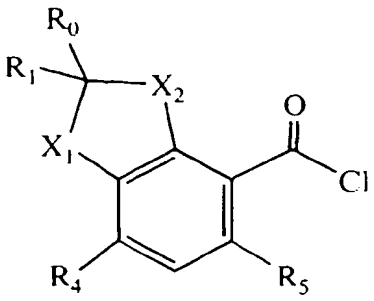
(IV)

19. A process according to claim 18, whereby the compound (IV) is prepared by heating a compound having the general formula (V) under basic conditions, optionally in the presence of a solvent.

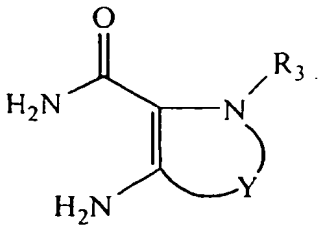


(V)

20. A process according to claim 19, whereby the compound (V) is prepared by reacting a compound having the general formula (VI) with a compound having the general formula (VII), optionally in the presence of a solvent and a base.



(VI)



(VII)

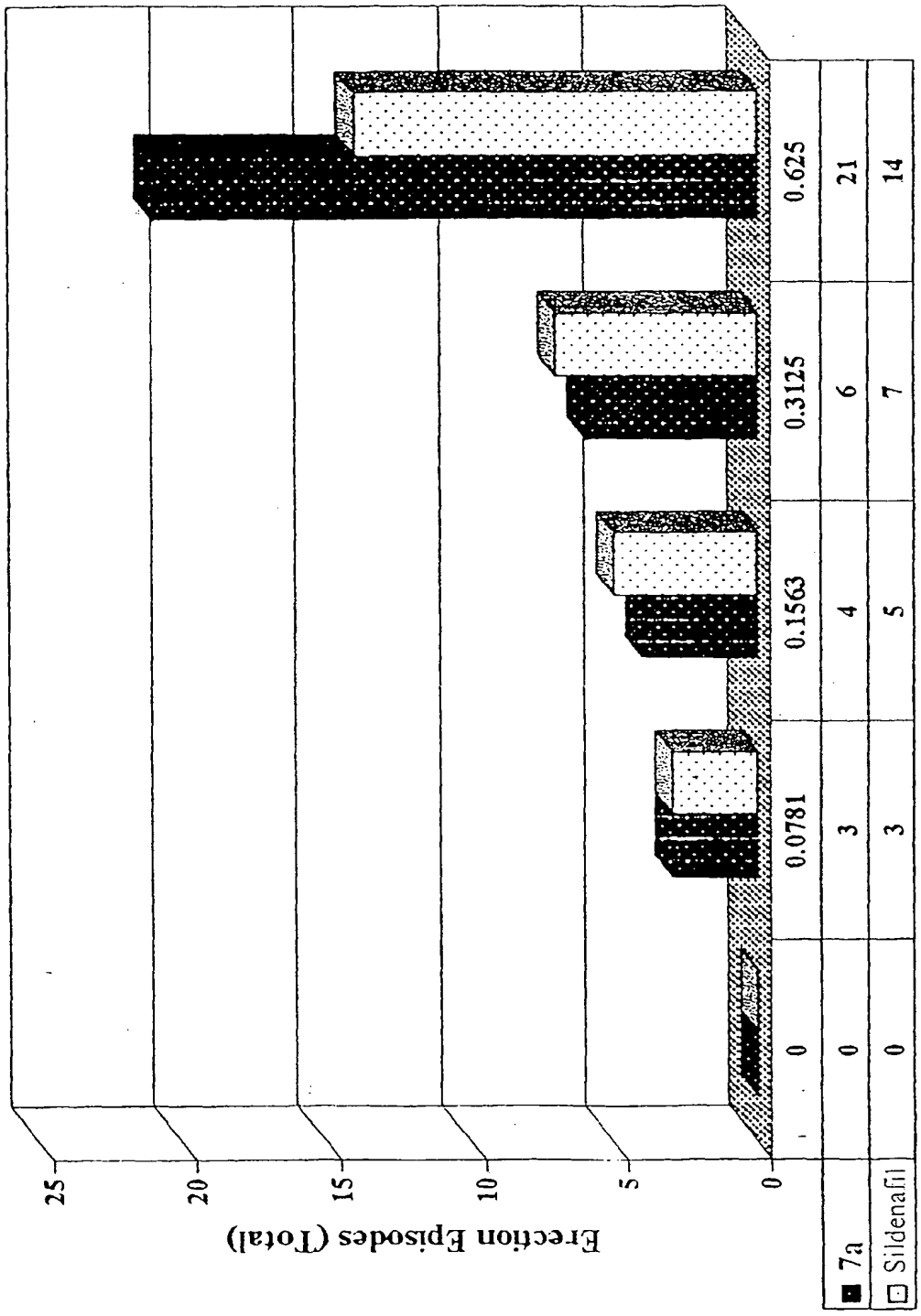


Fig. 1; Total number of erection episodes for 7a and sildenafil.

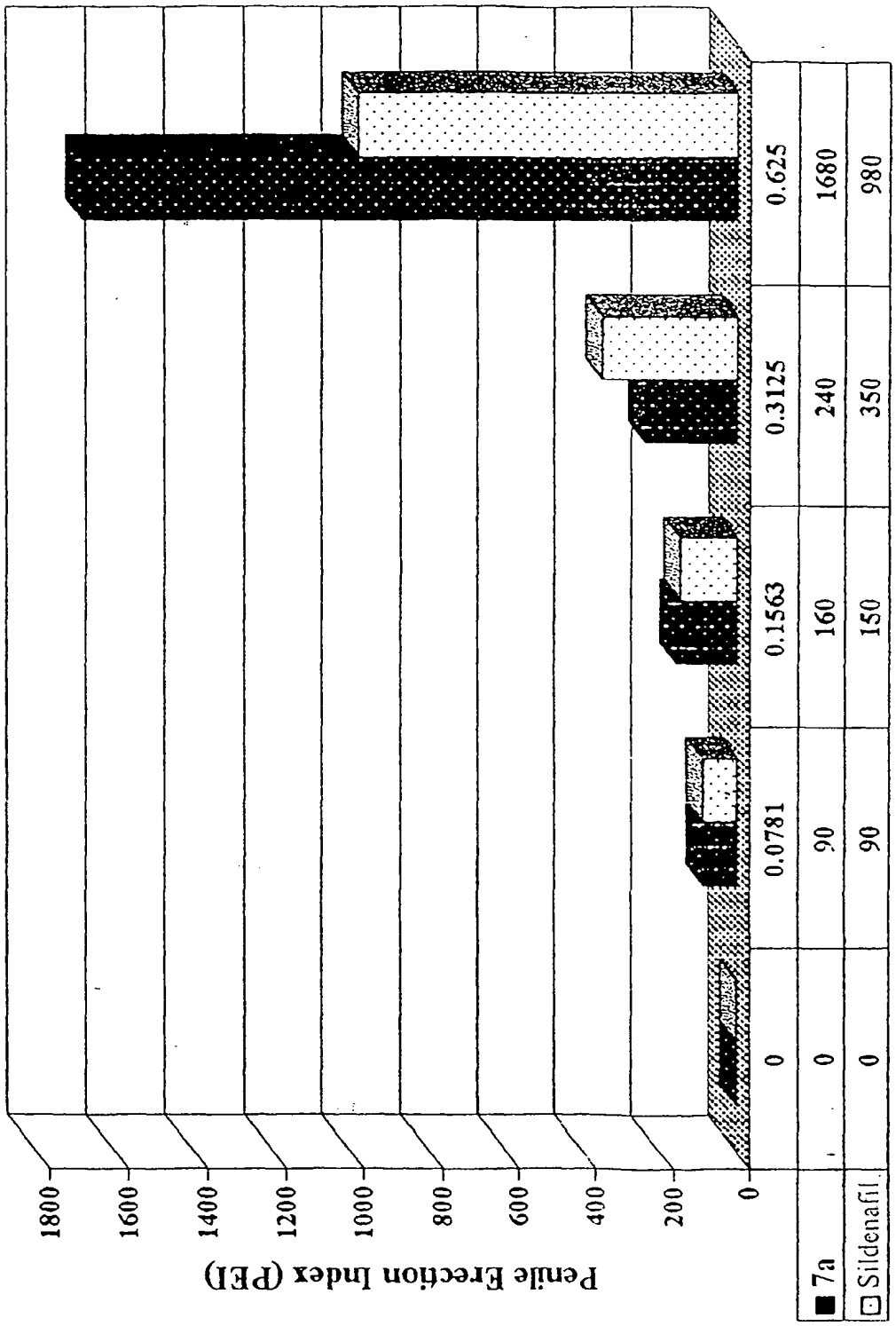


Fig. 2; Penile erection index for 7a and sildenafil.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 99 85 0097

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,A	WO 98 49166 A (PFIZER) 5 November 1998 (1998-11-05) * claims 1,12 * -----	1,14	C07D487/04 A61K31/519 C07D498/04 //(C07D487/04, 239:00,231:00)

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07D
A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

Although claim 16 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Place of search	Date of completion of the search	Examiner
THE HAGUE	29 November 1999	Alfaro Faus, I

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 85 0097

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29-11-1999

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WO 9849166 A	05-11-1998	AU 7644598 A	24-11-1998
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

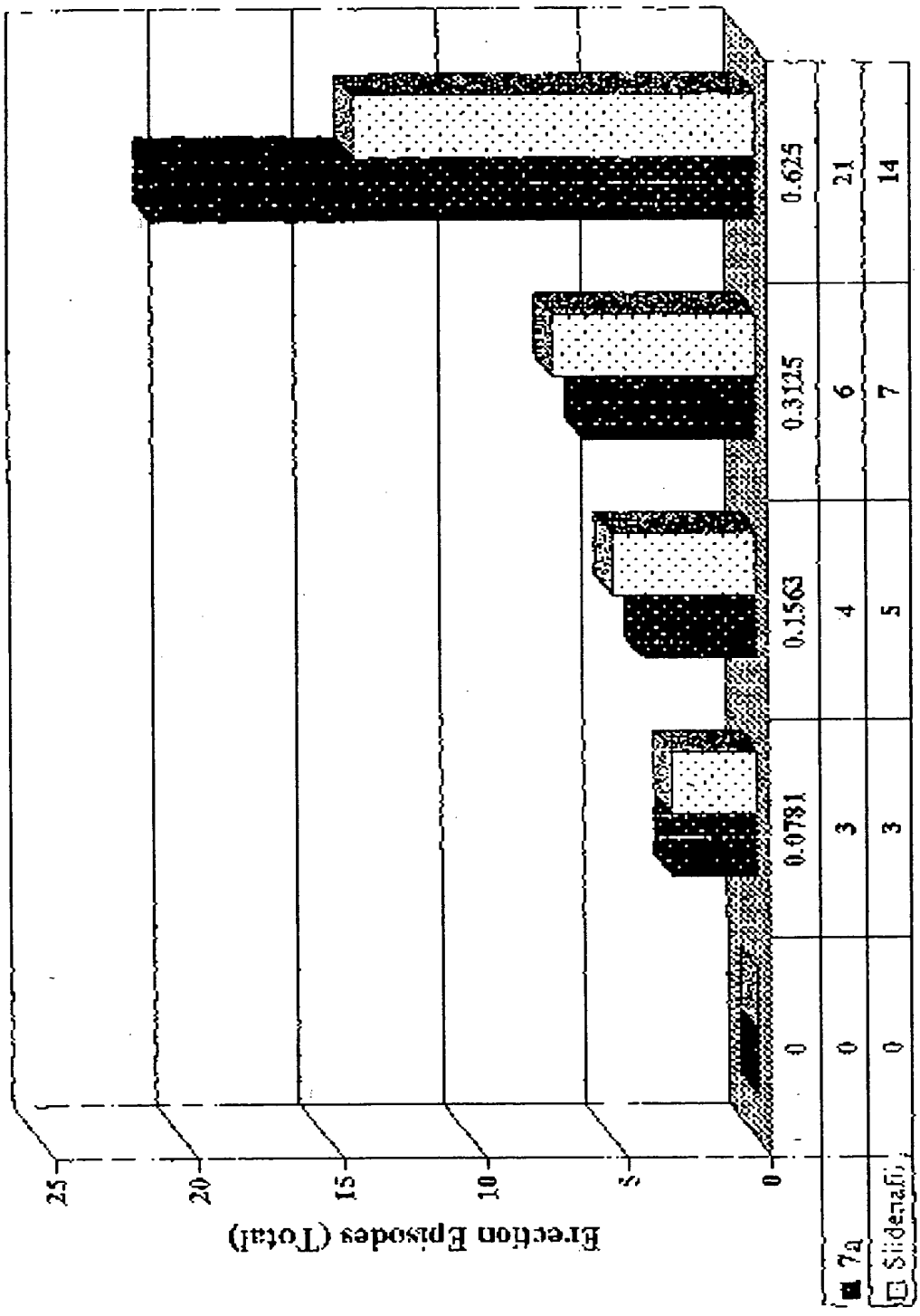

Fig. 1; Total number of erection episodes for 7a and sildenafil.

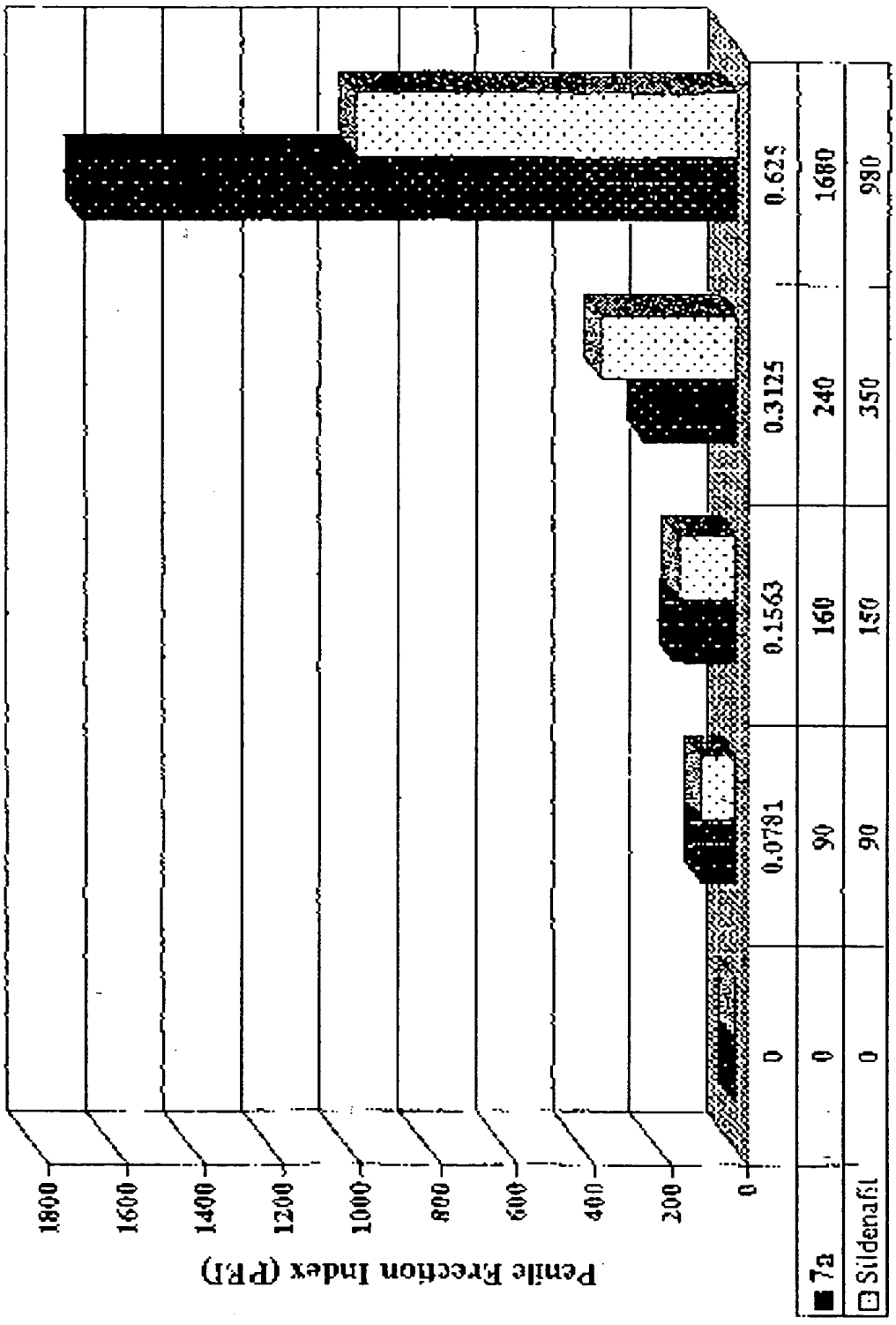

Fig. 2; Penile erection index for 7a and sildenafil.